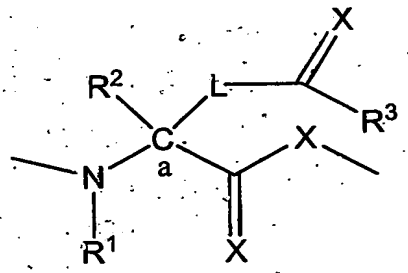
CLAIMS

We claim:

1. A composition comprising erythropoietin and an erythropoietin production inducing peptide (EPIP).
2. A composition comprising an EPIP.
3. The composition of claim 1, comprising a therapeutically effective amount of erythropoietin and EPIP.
4. The composition of claim 1, comprising a therapeutically effective amount of an EPIP.
5. The composition of claim 1, wherein the erythropoietin is recombinant erythropoietin.
6. The composition of any one of claims 1-5 wherein the EPIP comprises at least two residues having the formula I or II



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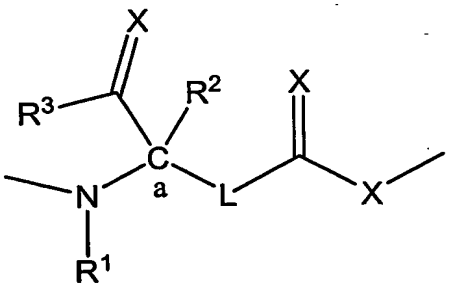


II

wherein

each X comprises, independently oxygen or sulfur;

L is not present or when L is present, L comprises oxygen, NR^4, or a substituted or unsubstituted methylene group, polyalkylene group,

polyether group, polyamide group, polyester group, polyimino group, aryl group, or polythioether group;

R^1, R^2, R^3 and R^4 comprises, independently, hydrogen, halide, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, aralkyl, alkoxy, hydroxyalkyl, alkoxyalkyl, a keto group, an ester group, a carbonate group, an aldehyde group, or a carboxylic acid group; and

the stereochemistry at carbon a is substantially R, substantially S, or a mixture thereof of R and S;

wherein the residues having the formula I and II are neutral or ionic, wherein each residue can have the formula I, each of the residues can have the formula II, or the residues can be a mixture of formulas I and II.

7. The composition of claim 6, wherein each X is oxygen.

8. The composition of claim 6, wherein R^1 and R^2 are hydrogen.

9. The composition of claim 6, wherein L comprises a polyalkylene group.

10. The composition of claim 6, wherein R^3 is hydroxyl, alkoxy, or OM, wherein M is a cationic salt.

11. The composition of claim 6, wherein each X is oxygen, R^1 and R^2 are hydrogen, R^3 is hydroxyl or OM, wherein M comprises a cationic salt, L is CH_2CH_2, and the stereochemistry at carbon a is substantially R or substantially S.

12. The composition of claim 6, wherein the residues have the formula I.

13. The composition of claim 6, wherein the EPIP comprises only residues having the formula I, formula II, or a mixture thereof.

14. The composition of claim 6, wherein the EPIP comprises poly-D-glutamic acid, poly-L-glutamic acid, poly-D-aspartic acid, poly-L-aspartic acid, or a mixture of both.

15. The composition of claim 14, wherein the EPIP is poly-D-glutamic acid.

16. The composition of claim 6, wherein the wherein the EPIP comprises at least two residues having a tethered carboxylic acid group, a tethered amide group, a tethered ester group or salt thereof.

17. The composition of claim 6, wherein the tether comprises a polyalkylene group, a polyether group, a polyamide group, a polyester group, a polyimino group, an aryl group, or a polythioether group.

18. The composition of claim 17, wherein the tether comprises a polyalkylene group.

19. The composition of claim 6, further comprising a pharmaceutically acceptable diluent, adjuvant or carrier.

20. The composition of claim 6, wherein the preservative comprises benzyl alcohol, a paraben and phenol, or a mixture thereof.

21. The composition of any one of the claims above, wherein the composition further comprises a buffering agent.

22. The composition of claim 21, wherein the buffering agent comprises citrate, phosphate, tartrate, succinate, adipate, maleate, lactate and acetate buffers, sodium bicarbonate, and sodium carbonate, or a mixture thereof.

23. The composition of any one of claims above, further comprising an isotonicity adjusting agent, wherein the isotonicity adjusting agent comprises sodium chloride, glycerol, mannitol, sorbitol, or a mixture thereof.

24. The composition of any one of the claims above, further comprising a pH adjusting agent that adjusts the pH of the solution within the range of 5-8.

25. The composition of any one of the claims above, further comprising human serum albumin.

26. The composition of any one of the claims above, wherein the composition is an aqueous solution, a non-aqueous suspension, or a dry powder.

27. The composition of any one of claims above, wherein the composition is in oral dosage form.

28. The composition of claim 6, further comprising fatty acid(s), surfactant(s), or enteric material, or a mixture thereof, wherein components are mixed in liquid phase and lyophilized.

29. The composition of any one of the claims above, wherein the composition is in injectable form.

30. A composition comprising cells derived either from a subject treated with EPIP or co-cultured *in vitro* with proximal tubular cells exposed to EPIP either *in vivo* or *ex vivo*, wherein the derived cells can be propagated *in vitro* and are capable of producing erythropoietin.

31. The composition of claim 30, wherein said EPIP is poly-D-glutamic acid , poly-L- glutamic acid, poly-D-aspartic acid, poly-L-aspartic acid, or a mixture of both.

32. The composition of claim 31, wherein said EPIP is poly-D-glutamic acid.

33. The composition of claim 30, wherein said cells produce 100 U or more of erythropoietin per 10^6 cells in 48 hours.

34. The composition of claim 32, wherein the cells are capable of producing 500 U or more of erythropoietin.

35. The composition of claim 32, wherein the cells are capable of producing 1000 U or more of erythropoietin.

36. The composition of claim 31, wherein the poly-D-glutamic acid is administered in the amount of about 50 mg/kg of body weight per day to 400 mg/kg of body weight per day.

37. The composition of claim 30, wherein the cells continue to express erythropoietin after exposure to the EPIP.

38. The composition of claim 30, wherein the cells are indirectly stimulated to produce erythropoietin by the EPIP.

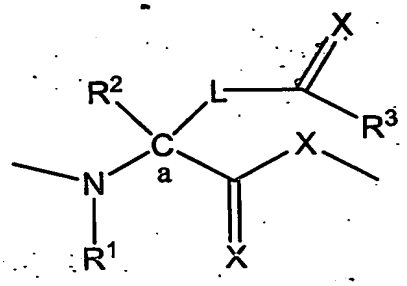
39. The composition of claim 30, wherein proximal tubular cells are treated with EPIP and in turn stimulate proliferation of erythropoietin producing cells.

40. A method of treatment comprising administering erythropoietin to a subject, wherein the erythropoietin is produced by the method of claim 74.

41. A method of treatment comprising administering erythropoietin and an EPIP to a subject.

42. A method of treatment comprising administering an EPIP to a subject.

43. The method of claim 42, wherein the EPIP comprises at least two residues having the formula I or II



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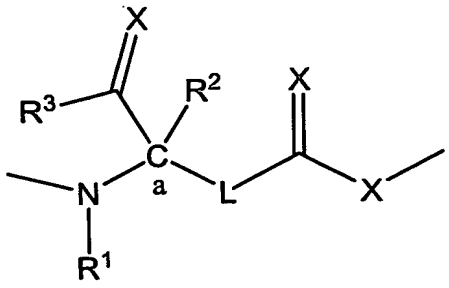

II

wherein

each X comprises, independently oxygen or sulfur;

L is not present or when L is present, L comprises oxygen, NR^4, or a substituted or unsubstituted methylene group, polyalkylene group, polyether group, polyamide group, polyester group, polyimino group, aryl group, or polythioether group;

R^1, R^2, R^3 and R^4 comprises, independently, hydrogen, halide, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, aralkyl, alkoxy, hydroxyalkyl, alkoxyalkyl, a keto group, an ester group, a carbonate group, an aldehyde group, or a carboxylic acid group; and

the stereochemistry at carbon a is substantially R, substantially S, or a mixture thereof of R and S;

wherein the residues having the formula I and II are neutral or ionic,

wherein each of the residues can have the formula I, each of the residues can have the formula II, or the residues can be a mixture of formulas I and II.

44. The method of claim 43, wherein each X is oxygen.

45. The method of claim 43, wherein R^1 and R^2 are hydrogen.

46. The method of claim 43, wherein L comprises a polyalkylene group.

47. The method of claim 43, wherein R^3 is hydroxyl, alkoxy, or OM, wherein M comprises a cationic salt.

48. The method of claim 43, wherein each X is oxygen, R^1 and R^2 are hydrogen, R^3 is hydroxyl or OM, wherein M comprises a cationic salt, L is CH_2CH_2, and the stereochemistry at carbon a is substantially R or substantially S.

49. The method of claim 43, wherein the residues have the formula I.

50. The method of claim 43, wherein the EPIP comprises only residues having the formula I, formula II, or a mixture thereof.

51. The method of claim 43, wherein the EPIP comprises poly-D-glutamic acid, poly-L-glutamic acid, poly-D-aspartic acid, poly-L-aspartic acid, or a mixture of both.

52. The method of claim 52, wherein the EPIP comprises poly-D-glutamic acid.

53. The method of claim 43, wherein the EPIP comprises at least two residues having a tethered carboxylic acid group, a tethered amide group, a tethered ester group or salt thereof.

54. The method of claim 53, wherein the tether comprises a polyalkylene group, a polyether group, a polyamide group, a polyester group, a polyimino group, an aryl group, or a polythioether group.

55. The method of claim 54, wherein the tether comprises a polyalkylene group.

56. The method of claim 43, wherein the method of treatment comprises treating anemia, Crohn's Disease, ulcerative colitis, chronic renal insufficiency, or end stage renal disease or any erythropoietin-responsive anemia.

57. The method of claim 43, wherein the treatment results in angiogenesis in the kidney.

58. The method of claim 43, wherein the method of treatment comprises treating organ or tissue transplantation subjects.

59. The method of claim 43, wherein the method of treatment comprises enhancing wound healing.

60. The method of claim 43, comprising treating a subject.

61. The method of claim 60, wherein the subject is a mammal.

62. The method of claim 60, wherein the subject is human.

63. The method of claim 43, wherein the erythropoietin and/or EPIP is administered by intravenous or intramuscular or subcutaneous or intraperitoneal injection.

64. The method of any one of claims 63, wherein the erythropoietin, EPIP, or erythropoietin and EPIP is administered orally or rectally.

65. The method of claim 43, wherein a mechanical device directs a stream of a therapeutically effective amount of poly-D-glutamic acid into the oral cavity of a mammal while the mammal is inhaling.

66. The method of claim 65, wherein the mechanical device is selected from the group consisting of a nebulizer, a metered dose inhaler, and a powder inhaler.

67. The method of claim 43, wherein the administration of poly-D-glutamic acid results in a red blood cell level of 5000 or more erythrocytes per uL of blood.

68. A method for testing a substance for the ability to stimulate erythropoietin production, the method comprising: a) contacting cells with the substance; and b) monitoring the cells for the production of erythropoietin.

69. The method of claim 68, further comprising comparing the production of erythropoietin produced in the presence of the substance to the amount of erythropoietin produced in the presence of an EPIP.

70. The method of claim 69, wherein the monitoring is Western blot analysis, or SDS PAGE, immunocytochemistry or Northern hybridization or in situ hybridization or enzyme-linked immunosorbent assay (ELISA) of enzyme-immuno assay (EIA) or radioimmunoassay (RIA).

71. The method of claim 67, wherein the cells produce between 100U and 1000U of erythropoietin.

72. A method for the production of erythropoietin, the method comprising: a) contacting cells in culture with a EPIP and b) harvesting erythropoietin from these cells.

73. A method for the production of erythropoietin, comprising a) administering a EPIP to a mammal and b) harvesting erythropoietin producing cells from the mammal.

74. A method for the production of erythropoietin comprising a) administering a EPIP to a mammal and b) harvesting proximal tubular cells from the kidney.

75. The method of claim any one of claims 68-74, wherein said EPIP comprises poly-D- glutamic acid.

76. The method of claim 74, wherein the erythropoietin is harvested by steps comprising: a) removing culture fluid from the cells; and b) isolating erythropoietin from the culture fluid.

77. The method of claim 76, wherein the erythropoietin is isolated from the culture fluid by using HPLC.

78. The method of claim 74, wherein erythropoietin is not isolated from the cell culture.

79. The method of claim 74 wherein the cells are mammalian cells.

80. The method of claim 79, wherein the cells are proximal tubular cells.

81. The method of claim 79, wherein the cells are peritubular insterstitial cells.

82. The method of claim 80, wherein co-cultures of proximal tubular cells cause the proliferation of fibroblast cells.

83. The method of claim 79, wherein the cells are kidney cells.

84. The method of claim 74, wherein at least 50% of the cells are producing erythropoietin.

85. Erythropoietin produced by the method of claim 74.

86. A method of identifying signal molecules associated with a proliferation of erythropoietin producing cells, comprising: a) treating a subject with a composition, b) identifying signal molecules which are responsive to the composition, c) screening the signal molecules individually or in combination to identify those signal molecules associated with a proliferation or erythropoietin producing cells.

87. The method of claim 86, wherein the composition is a EPIP.

88. The method of claim 87, wherein the said EPIP is poly-L-glutamic acid or poly-D-glutamic acid or a mixture of both.

89. The method of claim 86, wherein the signal molecules are monitored by Western blotting or Northern blotting or EIA or ELISA or RIA.

90. The method of claim 86, wherein the signal molecules are detected by gene array technology.

91. The method of claim 86, further comprising the step of d) using the signal molecules associated with a proliferation of erythropoietin to identify mechanisms of erythropoietin production.

92. A method of cell therapy comprising delivering an effective amount of erythropoietin producing cells to a subject.

93. The method of claim 92 wherein the cells are mammalian cells.

94. The method of claim 93, wherein the cells are proximal tubular cells.

95. The method of claim 93, wherein the cells are peritubular insterstitial cells.

96. The method of claim 93, wherein co-cultures of proximal tubular cells cause the proliferation of fibroblast cells.

97. The method of claim 93, wherein the cells are kidney cells.

98. A method of making cells that produce erythropoietin comprising administering to the cells an effective amount of an EPIP.

99. The method of claim 98, wherein the EPIP is administered to a cell that then stimulates the erythropoietin producing cell to produce erythropoietin.

100. The method of claim 99, wherein the cell that stimulates the erythropoietin producing cell is a proximal tubular cell.

101. The method of claim 98, wherein the cells continue to produce erythropoietin after exposure to EPIP.

102. A cell produced by the method of claim 98.